Remarks

- Claims 1, 4 – 9 are rejected for being unpatentable over Tabuchi, et al., in view of Donovan.

Examiner Interview

A telephonic interview was held between Examiner Kim and Applicant's representative Dr. Wilson on May 29, 2009. The Examiner is thanked for her courtesy and assistance during the interview. Proposed amendments to Claim 1 and 4 previously submitted by Dr. Wilson were discussed. Examiner Kim responded by suggesting folding Claim 4 into Claim 1 and deleting reference to Ischemia provoked cochlear excitotoxicity in Claim 1. Additionally, a personal interview with the Examiner is scheduled for October 2, 2009.

Claims Amendments

Claim 1 is amended.

1.132 Declaration

A Declaration under 37 CFR 1.132 by Dr. Richard Salvi, a noted expert in the field of audiology and tinnitus, is currently being formulated. The executed Declaration will be filed as a supplemental paper following the personal interview scheduled for October 2, 2009.

Comments Relating to Terminology and Propriety of Combining Tabuchi and Donovan References

As a preliminary point, Applicants note that although the cited Tabuchi, et al., and Donovan references have been combined to support a rejection under 35 USC 103, the propriety of the combination is not conceded. The basis for combining the two cited references appears on page 4 of the Office Action mailed April 1, 2009, which is reproduced below for convenience.

> … it would have been obvious to one of ordinary skill in the art to employ ketamine for the treatment of tinnitus induced by cochlear excitotoxicity provoked by ischemia because Tabuchi et al. teach the protective effect of ketamine in cochlear injury/dysfunction due to ischemic-reperfusion and because tinnitus is a disorder of the cochlea due to functional disturbances involving the auditory nerve as taught by Donovan. One would have been motivated to employ ketamine for the treatment of

> tinnitus in order to achieve an expected benefit of protection against cochlear damage due to ischemic-reperfusion resulting tinnitus [a] well known condition due to cochlear dysfunction by Donovan.

Thus, the linkage between the secondary and primary reference appears to be based primarily, if not exclusively, on the common usage of the term "cochlear dysfunction." That is, since both references discuss "cochlear dysfunction," it is assumed that one skilled in the art would be technically correct in assuming that the ischemia-reperfusion studies of Tabuchi, et al., necessarily resulted in tinnitus, and that the ketamine treatment regimen necessarily would be effective in the treatment of this condition. The referenced assumptions, which necessarily underlie the rejection as stated, are flawed assumptions as will be discussed in detail below.

Putting aside, for the moment, the flawed assumptions referred to in the preceding paragraph, Applicants note that terms "cochlear dysfunction" or "cochlear nerve dysfunction" are catchall terms relating to disturbances in the functioning of the hearing organ which result in a hearing impairment. There is no disclosure in the two cited references which suggests a common etiology associated with the two discussed forms of cochlear dysfunction. To this point, Tabuchi, et al., refer to ischemia-reperfusion induced cochlear dysfunction and Donovan reports clinical observations relating to tinnitus of unknown or unreported origin in humans. Applicants note that Donovan's target region is between the afferent dendrite and the primary auditory neurons whereas ketamine exerts its effect at the inner hair cell synaptic complex.

It is well known in the art that not all or even a large number of the different types of hearing impairment (*i.e.*, cochlear dysfunctions) are accompanied by tinnitus. A large number of people suffer from hearing loss and/or distorted hearing without being bothered by tinnitus at all. On the other side, there are also many people who have normal hearing (*i.e.*, no hearing impairment or cochlear dysfunction), but do suffer from tinnitus. Tinnitus can occur in individuals with normal hearing and no evidence of cochlear dysfunction involving the hair cells or auditory nerve (Barnea, G., Attias, J., Gold, S., Shahar, A. 1990. Tinnitus with normal hearing sensitivity: extended high-frequency audiometry and auditory-nerve brain-stem-evoked responses. *Audiology* 29, 36-45.; Del Bo, L., Forti, S., Ambrosetti, U., Costanzo, S., Mauro, D., Ugazio, G.,

Langguth, B., Mancuso, A. 2008. Tinnitus aurium in persons with normal hearing: 55 years later. *Otolaryngol Head Neck Surg* 139, 391-394). Conversely, many individuals with sensorineural hearing loss involving damage to the hair cells and auditor nerve do not experience tinnitus. Thus, and contrary to the Examiner's remarks ("…tinnitus which is cochlear nerve dysfunction…" and "…injury of the cochlea which causes tinnitus…" pending Action, pages 4 and 5), tinnitus is not necessarily associated with cochlear dysfunction and the logic underlying the proposed combination of references is improper.

Although the logic underlying the combination of the references improper, Applicants will now discuss the merits of the proposed combination, including the flawed assumptions referred to previously.

Rejection Under 35 USC 103

Claims 1 and 4-9 have been rejected as unpatentable over Tabuchi, et al., in view of Donovan. The cited Tabuchi reference discloses the treatment of cochlear dysfunction induced by transient ischemia. Guinea pigs were subjected to transient ischemia. The subject animals included an untreated control group, as well as a ketamine-treated group. Compound action potential (CAP) was determined for each group using methods described by Tabuchi, et al., (Hear. Res. 1998: 126: 28-36). CAP thresholds were measured before the administration of ketamine and 4 hours after the onset of reperfusion. Methods used in the control group were identical but for the absence of ketamine. Tabuchi report that the CAP threshold shifts were moderately ameliorated by ketamine. The Donovan patent is cited for the teaching that tinnitus is cochlear nerve dysfunction that is due to function disturbances of the synapse between cochlear hair cells and afferent dendrites of the auditory nerve.

In support of the obviousness rejection, the Patent Office states that:

> It would have been obvious to one of ordinary skill in the art at employ ketamine for the treatment of tinnitus induced by cochlear excitotoxicity provoked by ischemia because Tabuchi, et al., teach the protective effect of ketamine in cochlear injury/dysfunction due to ischemic-reperfusion which induces excitotoxicity and because tinnitus is a disorder of the

cochlea involving auditory nerve as taught by Donovan. Pending Action, page 7.

The Patent Office also states on page 4 of the pending Office Action that:

> Therefore, it would have been obvious to employ ketamine for the treatment of tinnitus which is cochlea nerve dysfunction in order to achieve a protection of cochlea ischemic injury involving auditory nerve such as tinnitus.

A glaring flaw in the logic underlying the stated rejection is that the guinea pigs of the Tabuchi, et al., reference were not shown to be suffering from tinnitus. In fact, at the time of the Tabuchi, et al., publication there was no behavioral assay, of the type reported in the subject patent application, which could be used to assess tinnitus. Rather, data reported by Tabuchi, et al., relates to CAP threshold shifts. The CAP is a physiological measure arising from the synchronous discharge of auditory nerve fibers in response to the onset of a suprathreshold sound stimulus. In contrast to the CAP, tinnitus is a subjective auditory sensation that occurs in the absence of controlled sound stimulation. Therefore the effects of ketamine on the CAP measurements in Tabuchi, et al., cannot teach one skilled in the art about the efficacy of using ketamine to treat subjective tinnitus, which is a subjective experience that occurs without sound stimulation.

Further, as noted previously, it is well known in the art that not all, or even a large number, of the different types of hearing impairment (*i.e.*, cochlear dysfunctions) are accompanied by tinnitus. In this regard, reference is made to Applicants' findings that even in cases of severe acute acoustic trauma that produces a much more profound hearing loss than that observed by Tabuchi, et al., only a minority of animals developed persisting tinnitus (see paragraphs 0060-0064 of subject patent application).

In light of the above consideration based on the combined teaching of Tabuchi, et al., and Donovan, one skilled in the art would have absolutely no basis for concluding that ketamine would have any effect whatsoever on tinnitus. A Declaration by Dr. Richard Salvi, a world-renowned expert in the filed of tinnitus, will provide expert

evidence to this effect. As previously mentioned, this Declaration will be filed as a supplemental paper following the scheduled personal interview.

Summary

Applicants respectfully request consideration of the pending specification in view of this Response. Any deficiency or overpayment should be charged or credited to Deposit Account No. 50-4514.

Respectfully submitted,

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